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10/622,301	07/18/2003	R. Scott Obach	PC10244B	7277

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EXAMINER	
JIANG, SHAOJIA ANNA	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 01/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/622,301	OBACH, R. SCOTT	
	Examiner	Art Unit	
	Shaojia A. Jiang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is a response to Applicant's amendment and response filed on October 21, 2004 wherein claims 2-3 are cancelled and claims 1 and 4-6 have been amended.

Currently, claims 1 and 4-6 are pending in this application.

Claims 1 and 4-6 as amended now are examined on the merits herein.

The provisional obviousness-type double patenting rejection of claims 1 and 4 as being unpatentable over claim 1 of copending Application No. 09/528,978 of record in the previous Office Action June 16, 2004, is withdrawn since the copending Application No. 09/528,978 is abandoned.

Applicant's amendment filed October 21, 2004 with respect to the rejection of claims 1-6 made under 35 U.S.C. 112 second paragraph for missing recitation, i.e., "effective amount " in claim 1 of record stated in the Office Action dated June 16, 2004 have been fully considered and found persuasive to remove the rejection since the claim has been amended by adding "effective amount ". Therefore, the said rejection is withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 4-6 as amended now are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the particular drug disclosed in claim 1 and the specification (see page 4), and co-administering the particular CYP2D6 inhibitors in claims 4-6 and disclosed in the specification (see page 4) employed in claimed method herein, does not reasonably provide enablement for the employment of the particular drug in combination with any CYP2D6 inhibitors in the claimed methods of the particular treatments herein.

Note that particular CYP2D6 inhibitors recited in claims 4-5 herein are deemed to be separate and patentably distinct compounds since they do not share any common core structures and are classified in different subclasses of class 514.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to a method of administering a combination herein for therapy.

The relative skill of those in the art: The relative skill of those in the art is high.

The breadth of the claims: The instant claims are deemed very broad since these claims on any CYP2D6 substrates in combination with any CYP2D6 inhibitors employed in the claimed method herein.

The amount of direction or guidance presented:

Functional language at the point of novelty, as herein employed by Applicants in claims 1-2, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997). The CAFC clearly states that "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405(emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus.." at 1406 (emphasis added).

In the instant case, the particular drug in combination with a CYP2D6 inhibitor recited in the instant claim are purely functional distinction. Hence, these functional recitations read on any compounds that might have the recited functions. However, the

specification merely provides those particular compounds for a CYP2D6 inhibitor for the claimed method of administering herein (see page 3 of the specification).

Thus, Applicants functional language at the points of novelty in claim 1 fails to meet the requirements set forth under 35 U.S.C. 112, first paragraph.

The predictability or unpredictability: the instant claimed invention is highly *unpredictable* as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully described genus, visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, except those particular compounds of formula disclosed in the specification, as discussed above in *University of California v. Eli Lilly and Co.* Hence, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having claimed functional properties in the claimed method of treatment herein.

One of skill in the art would clearly recognize that quinidine and ajmalacine are separate and patentably distinct compounds since they do not share any common core structures (see their structures taught at page 4 of the instant specification); quinidine and ajmalacine are classified in different subclasses of class 514, for example, quinidine

classified in 514/299, 311, whereas ajmalacine classified in 514/410, 413, 415. Thus, ajmalacine is not deemed to have same or substantial similar physiological activities and properties as quinidine does. Therefore the enabling evidence for quinidine enhancing the pharmacological effect of (2S,3S)-2 phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine in the declarations is not considered to represent ajmalacine having the same or substantially similar effects.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutic effects for the combination herein, side effects, and especially serious toxicity that may be generated by drug-drug interactions when and/or after administering to a host (e.g., a human) the *combination* of any compounds represented by CYP2D6 substrates and CYP2D6 inhibitors, and/or while the patient also administering other medicines. See text book "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed, 1996) page 51 in particular. This book teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right column of page 51) (emphases added).

In the instant case, in the absence of fully recognizing the identity of the members genus herein except those particular compounds of formula in the specification, one of skill in the art would not be able to fully predict the possible treatments herein and possible adverse effects occurring with many compounds having claimed functional properties and their combinations to be administered to a host in the claimed method herein.

Further, In the instant case, in the absence of factual evidence for ajmalacine, one of skill in the art would not be able to fully predict possible beneficial or adverse drug-drug interactions occurring with the combination of ajmalacine and (2S,3S)-2 phenyl-3-(2-methoxy-5-trifluoromethoxyphenyl)methylamino-piperidine to be administered to a human. Thus, the teachings of the book clearly support that the instant claimed invention is highly unpredictable.

Thus, the teachings of the "Goodman & Gilman's" book clearly support that the instant claimed invention is highly unpredictable.

The presence or absence of working examples and the quantity of experimentation necessary:

The record contains **no** evidence in support of enablement of the instant claimed method by administering the combination encompassed by the claims. Thus, the specification fails to provide clear and convincing evidence in sufficient support of the broad use of any compounds having those functions recited in the instant claims. As a result, necessitating one of skill to perform an exhaustive search for the embodiments of

any compounds having those functions recited in the instant claims suitable to practice the claimed invention.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors, the case *University of California v. Eli Lilly and Co.* (CAFC, 1997) and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in *undue experimentation* to test all compounds encompassed in the instant claims and their combinations to be administered to a host employed in the claimed methods of the particular treatments herein, with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 4-6 as amended now are rejected under 35 U.S.C. 103(a) as being unpatentable over Sands (5,716,961) in view of Benet et al. (5,567,592) or Sandyk (5,470,846) for same reasons of record stated in the Office Action dated June 16, 2004.

Sands discloses that the particular NMDA receptor antagonists of formula (I), in particular the instant compound, (1S, 2S)-1-(4-hydoxyphenyl)2(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol (see claim 8 and Example 1 at col.8), are neuroprotective agnets and useful in methods of treating neurological disorders (see col.1 lines 37-55).

Sands does not expressly disclose the employment of (1S, 2S)-1-(4-hydoxyphenyl)2(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol as a CYP2D6 substrate in mediating oxidative biotransformation in combination with quinidine or sertraline as a CYP2D6 inhibitor to be administered in a method for the major clearance mechanism in humans.

Benet et al. teaches the administration a drug that is the particular cytochromes P450, CYP2D6 substrate which is a member of CYP family, in mediating oxidative biotransformation for the major clearance mechanism in humans. See col.1-2. Benet et al. also teaches that CYP2D6 inhibitors such as quinidine, calcium channel blockers, and phenothiazines are useful as bioenhancers to increase the bioavailability of a pharmaceutical compound through the inhibition of cytochrome P450. See col.2 lines 46 – col.3 lines 25, and col.7. Benet et al. further teaches that a drug having activity of CYP3A (CYP3A substrate), another particular member of CYP family in combination with a CYP3A inhibitor which is not the same compound in the instant method for the improvement of drug bioavailability and major clearance. See col.9-11 Table 1.

Sandyk disclose that sertraline is a known serotonin reuptake inhibitor and useful in a method of treating neurological disorders (see col.9 lines 5-7, and abstract, col.1-7).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ (1S, 2S)-1-(4-hydoxyphenyl)2(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol in combination with quinidine as a CYP2D6 inhibitor or sertraline to be administered in a method for the major clearance mechanism in humans.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ (1S, 2S)-1-(4-hydoxyphenyl)2(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol in combination with quinidine as a CYP2D6 inhibitor or sertraline in a method for the major clearance mechanism in humans, since quinidine is a known CYP2D6 inhibitor and useful in a method for enhancing drug pharmacokinetic profile and the major clearance mechanism according to Benet et al. It is well known that CYP2D6 substrates mediate oxidative biotransformation for the major clearance mechanism in humans. Further, it is known that the employment of a drug having CYP3A activity within the same CYP family (a CYP3A substrate) in combination with a CYP3A inhibitor which is not the same compound is useful in the same method for improvement of the improvement of drug bioavailability and major clearance according to Benet et al. Therefore, one of ordinary skill in the art would have reasonably expected that quinidine, a CYP2D6 inhibitor would enhance drug bioavailability and major clearance of (1S, 2S)-1-(4-hydoxyphenyl)2(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol, a CYP2D6 substrate, when administering together.

Moreover, both (1S, 2S)-1-(4-hydoxyphenyl)2(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol and sertraline are known to be useful in treating neurological disorders.

Therefore, one of ordinary skill in the art would have reasonably expected that combining (1S, 2S)-1-(4-hydoxyphenyl)2(4-hydroxy-4-phenylpiperidin-1-yl)-1-propanol and sertraline both known useful for the same purpose, i.e., treating neurological disorders, would improve the therapeutic effects for treating the same diseases, and/or would produce additive therapeutic effects in treating the same. See *In re Kerkhoven*, 205 USPQ 1069, CCPA 1980.

Response to Argument

Applicant's arguments filed October 21, 2004 with respect to this rejection made under 35 U.S.C. 103(a) of record in the previous Office Action have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art as further discussed below.

Applicant's arguments are not found convincing, as noted that arguments of counsel cannot take the place of factually supported objective evidence. See, e.g., In re Huang, 100 F.3d 135,139-40, 40 USPQ2d 1685, 1689 (Fed. Cir. 1996); In re De Blauwe, 736 F.2d 699, 705, 222 USPQ 191, 196 (Fed. Cir. 1984). The burden is shifted to Applicant to show factually supported objective evidence to rebut the prima facie case of obviousness over the prior art.

Applicant is suggested to file a declaration under 37 CFR 1.132 with factual evidence such as testing data and figures to rebut the obviousness rejection. Note that evidence as to unexpected benefits must be "clear and convincing" *In re Lohr*, 137 USPQ 548 (CCPA 1963), and be of a scope reasonably commensurate with the scope of the subject matter claimed, *In re Linder*, 173 USPQ 356 (CCPA, 1972).

In view of the rejections to the pending claims set forth above, no claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

S. Anna Jiang, Ph.D.
Primary Examiner
Art Unit 1617
January 13, 2005